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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,772	07/31/2002	Malcolm Roy Brandon	78870/00004	7473

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
01/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/980,772	BRANDON ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,9-23,30-36 and 41-43* is/are pending in the application.

4a) Of the above claim(s) *16-19 and 31-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 9-15, 20-23, 30, 34-36 and 41-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's arguments filed May 17, 2007 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-4, 6, 9-23, 30-36 and 41-43 are pending. Claims 16-19 and 31-33 are withdrawn from consideration as to a nonelected invention. Claims 1-4, 6, 9-15, 20-23, 30, 34-36 and 41-43 are examined herein.

Each of claims 20, 21 and 23 at line 10 has misspelled "group." Applicant should correct this and review the claims for additional misspelled words and other typographical errors.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-23, 30, 34, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of generating a mammalian embryo or a mammalian transgenic embryo and methods of generating a mammalian pluripotent cell line comprising transferring a somatic cell nucleus into an oocyte, removing the nucleus, activating the one-cell embryo, permitting the embryo to grow to into a blastocyst, and isolating ES cells from the blastocyst, comprising preparing a reprogrammed diploid mammalian cell, activating and culturing the enucleated hybrid cell to a form an embryo, does not reasonably provide enablement for producing an embryo, tissue, organ or a mammal where the donor cell and the recipient cell, and in the case of generating a mammal, the surrogate mother are of different species and when the embryo is not activated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims as written are not enabled for their breadth.

With regard to activation, the art taught at the time of filing activation was necessary to cause the reconstituted embryo that is the hybrid cell, to begin cell division. For claims 2-23, 30, 34, 42 and 43 cell division is necessary to generate a cell line, a tissue, an organ, or mammal. There is no option to activate or not activate. Each of the claimed results requires more than the hybrid cell. Thus activation of the reprogrammed hybrid cell is necessary for enablement. The specification discloses strontium activation in the production of blastocysts and the isolation of a pluripotent cell line (specification, page 31, lines 7-9).

There is no evidence in the specification that the method claimed sufficiently reprograms a donor somatic cell nucleus sufficiently to support embryo growth or mammalian development. At the time of filing, the production of cloned offspring was regarded as the only evidence of reprogramming (Campbell, page 8, lines 41-47). Applicant has shown the reprogramming method is sufficient to cause chimeric mouse formation, but there is no evidence of an entire animal being produced where the donor somatic cell was treated by the claimed method (specification, page 32, lines 11-15). Thus, absent evidence of term birth, the methods claimed are not fully enabled.

Also with regard to producing a mammal, organs and tissues from the mammal, at the time of filing, cross-species nuclear transfer and the cloning of primates was not enabled at the time of filing. Meirelles demonstrates that methods of nuclear transfer where the nuclear material of *Bos indicus* is inserted into the oocyte of *Bos taurus* produces calves comprising the nuclear material of *Bos indicus* and the mitochondria of *Bos taurus*. Meirelles *et al*. teach that previous attempts to use the *Bos* oocyte as hosts for nuclear transfer from unrelated species allowed development to the blastocyst stage, and conclude that incompatibility among the nuclear and mitochondrial genetic systems is responsible for the early arrest. Meirelles also points to similar failures using *Mus caroli* and *Mus musculus* citing Dominko. Meirelles conclude stat in light of their results and the failures of the prior

art, that nuclear transfer across subspecies barriers is possible. (see Meirelles, pp. 351-355). In addition, the claims encompass methods of nuclear transfer when the oocyte is of a different species than the surrogate mother animal. Further, in the production of sheep goat chimeras, there were biases towards chimeras whose genotype and phenotype was most like that of the recipient, and that the successful production of chimeras resided in the neutralization of incompatibility between the chimeric embryos (Fehilly et al (1985), page 221, parag. 1). It is also noted the cloning of monkeys, a primate, by nuclear transfer had been successful when embryonic cells were the nuclear donor, not when somatic cells were used as nuclear donor (Mitalipov, abstract). Mitalipov further states, clearly, that somatic cell cloning, as is part of the present methods, has not been accomplished in primates (Mitalipov, page 1367, col. 2, parag, 3, lines 1-3). Simerly, states that in rhesus monkey NT units, DNA and microtubule imaging showed disarrayed mitotic spindles with misaligned chromosomes, which resulted in unequal chromosome segregation and aneuploid embryos (page 297, col. 2, parag. 1, lines 5-11). Therefore claims 20-23, 30, 34, 42 and 43 would not have been regarded as enabled by the skilled artisan at the time of filing without an undue amount of experimentation and lacking a predictable degree of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 9, 14 and 15 are confusing rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is confusing as it does not further limit claim 1, which states the donor cell or donor nucleus is a somatic cell or a somatic cell nucleus. A somatic cell is regarded by the

art as being a differentiated cell, where as a somatic stem cell gives rise to a differentiated cell. A somatic stem cell is not a species of somatic cell.

Claims 14 and 15 are confusing as the claims are to methods of reprogramming a somatic cell by formation of a heterokaryon. Claims 14 and 15 are not related to a method of reprogramming but a method of generating a pluripotent stem cell or an embryonic stem cell line is produced. Applicant should rewrite claims 14 and 15 independent of claim 1, 12 and 13.

Claim 15 does not have antecedent basis to claim 14 as there is no recitation of embryonic stem cell in claim 14. It is suggested claim 15 be rewritten to state wherein the pluripotent cell is an embryonic stem cell.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, 10-13, 21, 30, 34, 36 and 41-4are rejected under 35 U.S.C. 103(a) as being unpatentable over Czolowska et al. (1984) J. Cell Sci., Vol. 69, pp. 19-34 in view of Wakayama et al. (1998) Nature, Vol. 394, pp. 369-374.

Czolowska teaches the reprogramming of human thymocytes nuclear DNA, thymocytes being a somatic cell, where a human thymocyte is fused to a mouse oocyte arrested at metaphase II (MII), thereby introducing the thymocyte nucleus into the oocyte (page 21, parag. 5 and 6). A human thymocyte is a diploid mammalian donor cell and the mouse oocyte is a mammalian recipient cell. Czolowska states the thymocyte nuclei are reprogrammed as evidenced by the nuclei undergoing premature chromosome condensation

and nuclear swelling (page 27, parag. 2 and page 32, parag. 2, lines 4-6, and parag. 3). Czolowska states for mammals introduction of the nucleus prior to activation of the recipient oocyte provides the optimal conditions for nuclear transfer (page. 32, parag. 4, lines 5-7).

Wakayama differs from Czolowska in that Wakayama transfers the donor nucleus into an enucleated oocyte rather than nucleated oocytes as Czolowska. Wakayama teaches the removal of the nucleus from a mouse MII oocyte by a piezo-impact pipette drive unit (page 373, col. 2, lines 5-12). Wakayama offers motivation in stating the piezo-impact drive unit may contribute to high embryonic development rate because the manipulations are quick and efficient limiting trauma to the recipient oocyte and donor nucleus than other methods of fusion (page 373, col. 1, lines 11-16). Wakayama teaches a delay in oocyte activation after transfer of the donor nucleus yields greater cloned embyos and cloned mice (page 371, Table 3). Wakayama teaches embryonic, fetal and term development methods (page 373, col. 2, parags. 2 and 3).

The methods of Czolowska and Wakayama combined would lead to the formation of an embryonic cell that would be capable of forming a mouse embryo containing pluripotent embryonic cells.

Thus at the time of filing, it would have been obvious to the ordinary artisan to reprogram a donor nucleus by the method of Czolowska to form a heterokaryon, followed by enucleation by a piezo device, embryonic development and transfer to a surrogate mother for term development as taught by Wakayama to improve cloning efficiency. Both Czolowska and Wakayama offer sufficient motivation to combine as the level of experimentation in the art at the time of filing was high.

Claims 20, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over over Czolowska et al. (1984) J. Cell Sci., Vol. 69, pp. 19-34 in view of Cibelli et al. (1998) Science, Vol. 280, pp. 1256-1258.

Czolowska teaches the reprogramming of human thymocytes nuclear DNA, thymocytes being a somatic cell, where a human thymocyte is fused to a mouse oocyte arrested at metaphase II (MII), thereby introducing the thymocyte nucleus into the oocyte (page 21, parag. 5 and 6). The human thymocyte is a diploid mammalian donor cell and the mouse oocyte is a mammalian recipient cell. Czolowska states the thymocyte nuclei are reprogrammed as evidenced by the nuclei undergoing premature chromosome condensation and nuclear swelling (page 27, parag. 2 and page 32, parag. 2, lines 4-6, and parag. 3). Czolowska states for mammals introduction of the nucleus prior to activation of the recipient oocyte provides the optimal conditions for nuclear transfer (page. 32, parag. 4, lines 5-7).

Cibelli teaches the production of transgenic cow embryos and transgenic cows by nuclear transfer where the donor fibroblast has been genetically modified to contain a gene encoding a β-gal/GEO fusion protein (page 1256, col. 3, parag. 1, lines 1-8; page 1257, col. 1, parag. 1, lines 1-4 and parag. 2, lines 1-6). The method of Cibelli transferred the transgenic nucleus into an enucleated MII oocyte subsequently activated (1258, fn. 12).

Thus at the time of filing, it would have been obvious to the ordinary artisan to reprogram a transgenic donor nucleus by the method of Czolowska to form a heterokaryon, followed by enucleation, embryonic development and transfer to a surrogate mother for term development as taught by Cibelli improve cloning efficiency of transgenic mammals. Both Czolowska and Wakayama offer sufficient motivation to combine as the level of experimentation in the art at the time of filing was high.

Claims 1, 9, 12-15 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Czolowska et al. (1984) J. Cell Sci., Vol. 69, pp. 19-34 in view U.S. Patent 5,945,577 issued August 31, 1999, efd. January 10, 1997 (Stice).

Czolowska teaches the reprogramming of human thymocytes nuclear DNA, thymocytes being a somatic cell, where a human thymocyte is fused to a mouse oocyte arrested at metaphase II (MII), thereby introducing the thymocyte nucleus into the oocyte (page 21, parag. 5 and 6). The human thymocyte is a diploid mammalian donor cell and the mouse oocyte is a mammalian recipient cell. Czolowska states the thymocyte nuclei are reprogrammed as evidenced by the nuclei undergoing premature chromosome condensation and nuclear swelling (page 27, parag. 2 and page 32, parag. 2, lines 4-6, and parag. 3). Czolowska states for mammals introduction of the nucleus prior to activation of the recipient oocyte provides the optimal conditions for nuclear transfer (page. 32, parag. 4, lines 5-7).

Stice teaches hematopoietic cells as nuclear donors in nuclear transfer methods (col. 8, lines 9-16). Stice further teaches the transfer of nuclear donors into MII enucleated oocytes for embryonic development (col. 7, lines 9-26). Stice further teaches the recipient cell to be an enucleated human oocyte (col. 4, lines 30-33). Stice also teaches the production of an ICM cell line from the ICM cells of a blastocyst (col. 5, lines 43-55 and col. 17, lines 22-26). At the time of filing it was common knowledge in the art that diploid cells had a better success rate than aneuploid cells in cloning mammals.

Thus at the time of filing, it would have been obvious to the ordinary artisan to reprogram a donor nucleus by the method of Czolowska to form a heterokaryon, followed by enucleation and embryonic development as taught by Stice to improve cloning efficiency and/or to produce ICM cell lines. Both Czolowska and Stice offer sufficient motivation to combine as the level of experimentation in the art at the time of filing was high.

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matveeva et al. (1998) Molec. Reprod. Devel., Vol. 50, pp. 128-138, Tada et al. (1997) EMBO J., Vol. 16, pp. 6510-6520 or Rousset et al. (1983) Devel. Biol., Vol. 96, pp. 331-336 in view of Wakayama et al. (1998) Nature, Vol. 394, pp. 369-374.

Matveeva teaches the reprogramming of mouse spleenocytes by fusion with mouse ES cells as evidenced by the hybrid cells forming EB's in vitro and developing endoderm, ectoderm and mesodermal structures (page 134, col. 1, parag. 2, lines 1-13). Matveeva also teaches the production of chimeric mice by injecting the hybrid cells into mouse blastocysts (page 135, col. 1, parag. 1). The chimeric mice failed to produce offspring because of an abnormal number of X chromosomes (page 137, col. 1, parag. 2, lines 15-18).

Tada teaches the reprogramming of thymocytes isolated from ROSA26 mice by fusion with mouse EG cells as the hybrid cells contributes to tissue of all three germ layers in chimeric mice (page 6515, col. 2, parag. 2, line 2 to page 6516, col. 1, line 2). Tada states the full developmental potential is restricted because the chimeric embryos are tetraploid (page 6516, col. 1, lines 2-4). Tada further states the reprogramming activity of EG cells is comparable to that in PCG's (page 6517, col. 2, lines 1-2).

Rousset teaches mouse EC cells reprogram mouse thymocytes by the presence of all three germ layers in tumors resulting when mice were injected with the hybrid cells (page 334, col. 1, parag. 3, lines 3-5).

Wakayama differs from Matveeva et al., Tada et al. and Rousset et al in that Wakayama transfers the donor nucleus into an enucleated oocyte rather than nucleated oocytes as Czolowska. Wakayama teaches the removal of the nucleus from a mouse MII oocyte (page 373, col. 2, lines 5-12). Wakayama teaches a delay in oocyte activation after transfer of the donor nucleus yields greater cloned embyos and cloned mice (page 371,

Table 3). Wakayama teaches embryonic, fetal and term development methods (page 373, col. 2, parags. 2 and 3).

Thus at the time of filing, it would have been obvious to the ordinary artisan to reprogram a donor nucleus by the method of et al., Tada et al. and Rousset et al to form a heterokaryon and adopt the embryonic development and transfer to a surrogate mother for term development as taught by Wakayama to improve cloning efficiency. Both Czolowska and Wakayama offer sufficient motivation to combine as the level of experimentation in the art at the time of filing was high.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 6:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

December 21, 2007